Hemolytic disease of the fetus and newborn: awareness precedes change

Winter, D.P. de


CHAPTER
9

Antenatal Risk Estimation For Exchange Transfusions In Neonates With Hemolytic Disease Of The Fetus And Newborn In A Changing Treatment Landscape: A Multicenter, Retrospective Cohort Study

Derek P. de Winter, Masja de Haas, Christian V. Hulzebos, Michaël V. Lukens, Sandra A. Prins, Jasper V. Been, Esther J. d'Haens, Daniël C. Vijlbrief, Sabine L.A.G. Vrancken, Amanda M.P. Trompenaars, Huib Ceelie, Lieke M.J. van Zogchel, Annemiek M.C.P. Joosen, Clemens B. Meijssen, J.L.A.M. van Hillegersberg, Janneke C. Zant, Maaike C. van Rossem, Ron van Beek, Helene G. Stas, Clare E. Counsilman, F.R. Knol, I.A.M. Schiering, Gerdina H. Dubbink-Verheij, E.J.T. (Joanne) Verweij, Enrico Lopriore, for the WISE investigators

Published in Transfusion, 2025 Dec

ABSTRACT

Background: Neonates with hemolytic disease of the fetus and newborn (HDFN) may require exchange transfusions (ET) for severe hyperbilirubinemia. We evaluated if ET in neonates with HDFN was associated with the maximum maternal titer and antibody-dependent cellular-cytotoxicity (ADCC), and we determined the change in number of hospitals performing ET in the Netherlands.

Study design and methods: National, multicenter analysis of neonates for whom an ET product (c.q. reconstituted whole blood) was ordered between Jan 1, 2011 and Dec 31, 2021 in the Netherlands. To quantify the ET risk, we retrieved maternal serological test results for cases with an ET for non-ABO HDFN (numerator) and from all alloimmunized pregnancies (denominator). Current and past ET practices were assessed with a questionnaire.

Results: Twenty-four participating centers ordered 1564 of the total 1824 (84%) ET products in the 11-year study period. We identified 627 patients for whom a product was ordered, among these 111 (17.7%) received ET for HDFN. We found increasing ET rates in D-mediated HDFN from 0.9% (5/558) when maximum titers were ≤1:32 to 19.6% (18/92) if titers were 1:512. Rates of ET increased from 1.1% (9/823) if the maximum ADCC was <50% to 18.7% (72/386) if the ADCC was ≥50%. The number of hospitals practicing ET nowadays was 36.7% (18/49), a 56.1% decline compared to before 2010 (41/49).

Discussion: Antenatal serological tests may aid caregivers to anticipate the need for ET in neonates with non-ABO HDFN. We found a substantially altered treatment landscape with considerably fewer Dutch hospitals performing ET.

INTRODUCTION

Identification and timely treatment of pregnancies at-risk of fetal anemia due to hemolytic disease of the fetus and newborn (HDFN) has markedly improved in past decades.[1-3] HDFN is a disease in which maternal alloantibodies may destroy fetal erythrocytes, potentially causing fetal anemia.[4] Whereas antenatal management focuses on timely detecting and treating fetal anemia with intrauterine transfusions (IUT), postnatal management revolves around treating hyperbilirubinemia with intensive phototherapy.[1,3] In severe cases, exchange transfusions (ET) may be required to lower hazardous bilirubin levels. ETs are complex and invasive procedures with relatively high morbidity rates.[1,3] Double-volume exchange transfusions (160-180 mL/kg), performed through either a single-site central venous access or through an arterial and central venous access, can successfully lower bilirubin levels, remove maternal IgG and replace neonatal antigen-positive erythrocytes with antigen-negative donor erythrocytes.[1] Common adverse events associated with exchange transfusions include thrombocytopenia (31–90%), hypocalcemia (1–47%), leukocytopenia (33%), and sepsis (10%).[1] Due to preventative measures, such as anti-D immunoprophylaxis and precise blood group matching in transfusions, the prevalence of HDFN has dramatically decreased in high-income countries.[4] In addition, the availability of intensive phototherapy as primary treatment for severe hyperbilirubinemia has decreased the need for ETs.[5] As a consequence, ETs for severe hyperbilirubinemia due to HDFN may be increasingly rare[6-10], clinical experience with this complex procedure may decrease and fewer caregivers may be capable of safely performing ETs. Antenatal determination of the risk of ETs is imperative to anticipate a possible need for ETs and guide the location and timing of the delivery of neonates severely affected by HDFN.

We performed a national study in the Netherlands to assess if the need for an ET in neonates with HDFN could be estimated antenatally using the maximum alloantibody titer and/or antibody-dependent cellular cytotoxicity (ADCC) test determined in maternal blood. Additionally, we aimed to assess the national landscape of ETs and compare the past and current use of ET in the Netherlands through a questionnaire for pediatricians.

METHODS

National identification and management of at-risk pregnancies

In the Netherlands, serological monitoring for pregnancies with red blood cell alloimmunization is centralized at the national reference laboratory, Sanquin, Amsterdam, and the University Medical Center Groningen (UMCG). Obstetrical care

for alloimmunized pregnancies is centralized at the Leiden University Medical Center (LUMC) which is the national referral center for fetal therapy and IUTs. Briefly, all pregnant women are offered free screening for red blood cell antibodies with a coverage close to 100%.[4] Repeat serological risk stratification for fetal anemia is performed in case of a positive screening result in addition to a positive fetal genotyping result or in case of paternal homozygosity for the implicated antigen. The antibody titer, as a quantity measurement, and the antibody-dependent cellular cytotoxicity (ADCC) test, as a measurement of hemolytic activity[11], are performed at regular intervals among alloimmunized pregnancies. The antibody titer is determined through sequential dilution of maternal serum in an indirect antiglobulin test in tubes using C-c+D+E+e- erythrocytes (ccDEE, R2R2, double-dose D-antigens). The highest titer is the dilution in which the indirect antiglobulin test is positive, reported as 1:1, 1:2, 1:4 and so forth. The monocyte-mediated ADCC is performed by in-vitro monocyte-mediated hemolysis of Chromium-51 labelled red blood cells, through incubation with undiluted maternal serum. The ADCC level is determined by the amount of Chromium-51 that is released through hemolysis that is expressed as a percentage reaching from <10% to a maximum of >80%. The higher the percentage, the more hemolysis may be expected.[11] Maternal antibody titer and ADCC results are reported to the treating physician and consultants in laboratory medicine and stored in the patient's medical record throughout pregnancy. When tests are suggestive of a risk of fetal anemia and a potential need for IUTs based on predetermined cut-off values[11,12], pregnancies are referred to the LUMC for monitoring and treatment if required.

During the study period, the national hyperbilirubinemia guideline advises a double-volume ET in case of exceeding the predetermined total serum bilirubin of the ET treatment threshold, that is dependent on postnatal age and risk-factors, comparable to the American Academy of Pediatrics guideline 2004.[13] All participating centers followed this guideline. In the Netherlands, intravenous immunoglobulins (IVIG) to delay or prevent an impending ET are not routinely used. However, IVIG administration may be considered in case of total serum bilirubin levels reaching ET treatment thresholds despite intensive phototherapy. Nevertheless, IVIG is rarely used in severe neonatal hyperbilirubinemia.

Study design, data collection and population

We performed a national, multicenter, retrospective, observational cohort study to evaluate if the need for an ET in neonates with HDFN could be estimated antenatally using the maximum maternally alloantibody titers and ADCC test. We retrieved data from two sources to assess the potential of maternal antibody titers and ADCC to estimate

the risk of ET. We first acquired pseudonymized data from the Transfusion Medicine Unit at Sanquin on all ET products (c.q. reconstituted whole blood exchange transfusions) ordered in The Netherlands between January 1st, 2011 and December 31st, 2021 and invited all Dutch hospitals that ordered at least one ET product to participate. In the Netherlands, the blood supply is centralized into a single collection and distribution agency with a 24/7 service for ET products. Ordered ET products were then locally linked to the corresponding patient. Data from medical records was then retrieved by local investigators and entered in an online CastorEDC electronic case report form (eCRF). Data consisted of sex of the newborn, gestational age at birth, birthweight, indication for ordering ET products, serological measurements if applicable, and usage of ET products. The eCRF contained build-in validations and remaining inconsistencies or missing data were checked with local investigators. Neonates with hyperbilirubinemia due to non-ABO HDFN were included for analyses in this manuscript. We excluded neonates with severe congenital abnormalities and neonates who participated in a phase 2 clinical trial of a new drug for the treatment of HDFN (NCT03842189) from analyses in this manuscript as this may confound the postnatal risk of ETs.

Secondly, we retrieved a list of all alloimmunized pregnancies and the corresponding maximum maternally determined alloantibody titer in the study period from Immunohematology Diagnostics Sanquin and UMCG to estimate the risk of ETs in all alloimmunized pregnancies.

The study is reported according to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

National questionnaire on exchange transfusions

To investigate the current and past use of ET in the Netherlands, we invited pediatricians from all Dutch hospitals to fill out an eight-item questionnaire on current and past performance of ETs and preparedness to deliver neonates with HDFN at risk of severe hyperbilirubinemia with an imminent ET. The questionnaire was developed by authors Derek P. de Winter and Enrico Lopriore, and then approved by Masja de Haas, Joanne Verweij, Christian V. Hulzebos. The questionnaire consisted of close-ended questions with free text-options and could be completed within 5 minutes. We refer to the supplementary appendix for specific details. We assessed whether centers that currently do not perform ETs did perform this procedure before the study period. All Dutch hospitals received a primary invitation in December 2022, and those that did not respond within four weeks received a secondary invitation in January 2023. A third and final invitation was sent out in March 2023.

Statistical analysis

Continuous data was presented as median [interquartile range] and categorical data as proportions. As the ADCC may not have been repeated during pregnancy once the value reached the predetermined cut-off value of 50% in D-mediated HDFN or 30% in other types[11,12], we created two groups stratifying for these cut-off values. Receiver operating characteristic curve analysis, with accompanying negative- and positive-predictive values, was performed to assess the sensitivity and specificity of the ADCC and titer in correctly identifying neonates with ETs. To explore temporal changes in the ET landscape, we assessed the number of hospitals performing ETs currently and before 2010.

Ethical considerations

The non-WMO medical review committee of the LUMC reviewed the study and confirmed that the Medical Research Involving Human Subjects Act did not apply. The study adhered to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013; version 2013), complied with the General Data Protection Regulation (GDPR, Dutch: Algemene verordening gegevensbescherming, AVG), and the 'Code of Conduct for Health Research'. We received approval from local institutional review boards or ethical committees of participating centers. Informed consent was obtained by local investigators when required.

RESULTS

Characteristics of participating centers

Of all 72 Dutch hospitals, 55 (76.4%) ordered a total of 1923 ET products during the 11-year study period. After excluding two centers, a total of 53 hospitals that ordered 1859 products were invited. A total of 24 (45.3%) hospitals agreed to participate, including all nine neonatal intensive care units (NICU), 14 non-NICU hospitals, and one pediatric oncology hospital (Figure 1 and Supplementary Table). The 24 participating hospitals ordered 1564 (84.1%) of 1859 ET products within the study period.

Characteristics of included neonates

A total of 627 patients for whom an ET product was ordered were identified. Among these, ET products were ordered for 145 (23.1%) neonates with HDFN of which 111 (76.6%) actually received an ET (Table 1). In most of these 111 neonates, HDFN was primarily caused by anti-D (85/111, 76.6%), followed by anti-c (19/111, 17.1%), anti-E

(3/111, 2.7%), anti-C (1/111, 0.9%), anti-K1 (Kell) (1/111, 0.9%), anti-Wra (1/111, 0.9%) and anti-Jkb (1/111, 0.9%). In this group, 88 neonates (79.3%) were treated with one ET, 19 (17.1%) with two and five neonates (4.5%) with three or more. IVIG was administered to a total of five (5/145, 3.4%) neonates for whom an ET product was ordered. This included four neonates with D-mediated HDFN who did not receive an ET and one neonate with c-mediated HDFN who did receive an ET.

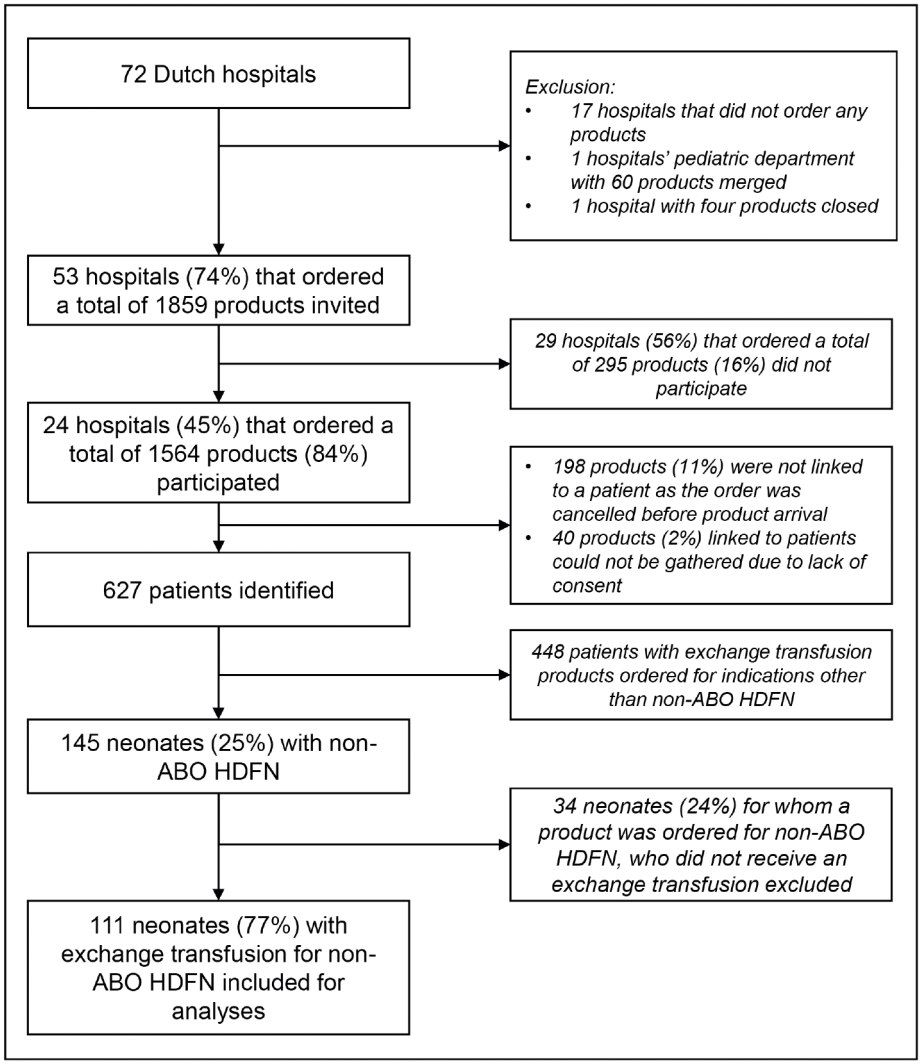

Figure 1: Flowchart showing the study population.

ET products were ordered for other indications, such as ABO-incompatibility or severe leukocytosis, among other indications, in 448 patients. The characteristics of these patients have been described previously.[14]

Table 1: Baseline clinical characteristics of neonates with HDFN and an exchange transfusion.

	Neonates with HDFN and exchange transfusion (n = 111)
Primary alloantibody	
Anti-D only	40/111 (36.0%)
Anti-D and others	45/111 (40.5%)
Anti-c only	14/111 (12.6%)
Anti-c and others	2/111 (1.8%)
Others	10/111 (6.3%)
IUT	25/111 (22.5%)
Number of IUTs	2 [1-3]
*Gestational age at first IUT**	30.5 [28.7-32.4]
Anti-D only	12/25 (48%)
Anti-D and others	11/25 (44%)
Anti-c only	1/25 (4%)
Anti-c and others	1/25 (4%)
Gestational age at birth	37.0 [35.6-37.5]
Birthweight (grams)	2970 [2660-3320]
Sex (% female)	47/111 (42.3%)

*known in 24/25 neonates with HDFN and an exchange transfusion that received an intrauterine transfusion antenatally.

Characteristics of alloimmunized pregnancies

A total of 1,901,734 children were liveborn in the study period in The Netherlands based on data from the Dutch Central Statistical Office. At our national reference laboratory, a total of 1247 pregnancies (0.06%) with primarily D-alloimmunization and an anti-D titer of ≥1:1 were identified within the study period. A total of 665 pregnancies (0.03%) with primarily c-alloimmunization with an anti-c titer ≥1 were identified.

Frequency of exchange transfusions based on maternal serology

The overall frequency of ETs was 6.8% (85/1247) in D-mediated HDFN and 2.4% (16/665) in c-mediated HDFN. Tables 2 and 3 show the ET frequency as part of the total number of pregnancies with a specific maximum maternal alloantibody titer and maximum maternal ADCC.

The maximum maternal titer or ADCC was missing in 4/85 (4.7%) neonates with an ET for D-mediated HDFN. In the remaining 81 neonates, rates of ETs increased from 0.9% (5/558) in maximum maternal titers ≤1:32 to 19.6% (18/92) in 1:512, with a relative decline in the rate of ETs to 13.6% (11/81) among titers ≥1:1024. ET rates in D-mediated HDFN increased from 1.1% (9/823) if the maximum maternal ADCC was <50% to 18.7% (72/386) if the ADCC was ≥50% (Table 2).

Table 2: Exchange transfusion frequency in D-mediated HDFN

Neonates with D-mediated HDFN and exchange transfusion* (n = 81)			
Maximum maternal anti-D titer	**Overall**	**ADCC <50%**	**ADCC ≥50%**
≤1:32	0.9% (5/558)	0.3% (2/555)	100% (3/3)
1:64	4.8% (7/143)	4.2% (5/118)	8.0% (2/25)
1:128	9.2% (17/184)	1.1% (1/89)	16.8% (16/95)
1:256	17.2% (26/151)	0% (0/41)	23.6% (26/110)
1:512	19.6% (18/92)	7.7% (1/13)	17.7% (14/79)
≥1:1024	13.6% (11/81)	0% (0/7)	14.9% (11/74)

Data presented as percentage and (number of neonates with an exchange transfusion / total number of pregnancies with the specific maximum antibody titer and ADCC value. *Maximum maternally determined titer and/or ADCC was unknown in 4/85 neonates with an exchange transfusion for D-mediated HDFN, including one neonate with D-mediated HDFN who was excluded from this analysis, as the diagnosis was unknown antenatally.

Similarly, in c-mediated HDFN we found increasing rates of ETs with increasing titers from 0.7% (4/559) in titers ≤1:32 to 12.5% (4/32) in 1:128 (Table 3). However, higher maximum maternal ADCC values in c-mediated HDFN were less distinctive for a higher ET frequency compared to D-mediated HDFN. The prevalence of ETs in other types of alloimmunization was too low to determine frequencies based on maternal serology. Table 4 shows the characteristics of these pregnancies.

Table 3: Exchange transfusion frequency in c-mediated HDFN per maximum maternal anti-c titer and maximum maternal ADCC result

Neonates with c-mediated HDFN and exchange transfusion* (n = 11)			
Maximum maternal anti-c titer	**Overall**	**ADCC <30%**	**ADCC ≥30%**
≤1:32	0.7% (4/559)	0.5% (3/548)	9.1% (1/11)
1:64	3.3% (2/60)	4.5% (2/44)	0% (0/16)
1:128	12.5% (4/32)	7.1% (1/14)	16.7% (3/18)
1:256	10.0% (1/10)	25.0% (1/4)	0% (0/6)
1:512	0% (0/3)	0% (0/1)	0% (0/2)
≥1:1024	0% (0/1)	0% (0/1)	NA (0/0)

Data presented as percentage and (number of neonates with an exchange transfusion / total number of pregnancies with the specific maximum antibody titer and ADCC value.
*Maximum maternally determined titer and/or ADCC was unknown in 5/16 neonates with an exchange transfusion for c-mediated HDFN.

Table 4: Characteristics of neonates with an exchange transfusion for less frequently found types of alloimmunization.

Case	Primary alloimmunization and maximum titer	Additional antibodies and maximum titer	Maximum ADCC	Gestational age at birth
1	Anti-E (1:128)	Anti-c (1:16)	70	37+2
2	Anti-E (1:256)	Anti-c (1:1), anti-Fy^{a} (unknown)	>80	33+5
3	Anti-E (1:256)	Anti-c (1:64)	55	36+5
4*	Anti-E (unknown)	*Not applicable*	Unknown	37+0
5	Anti-E (1:64)	*Not applicable*	20	29+2
6	Anti-C (unknown)	Anti-E (unknown)	Unknown	38+5
7	Anti-C (unknown)	Anti-Cw (unknown)	<10	40+1
8	Anti-K1 (1:128)	*Not applicable*	65	34+2
9*	Anti-Wra (unknown)	*Not applicable*	Unknown	38+1
10*	Anti-Jk^{b} (unknown)	*Not applicable*	Unknown	40+2

*Alloimmunization was unknown antenatally

The receiver operating characteristics curves for ET in D-mediated HDFN showed an area under the curve of 0.768 (95%-CI 0.728-0.808) for the maximum maternal titer and 0.836 (95%-CI 0.804-0.868) for the maximum maternal ADCC (Figure 2). At a cut-off of a maximum maternal titer of ≥1:256, minimizing false-negatives, the negative-predictive value was 96.7% and the positive-predictive value 15.7%. At a cut-off of the maximum maternal ADCC at ≥50%, the negative-predictive value was 98.9% and the positive-predictive value 18.7%.

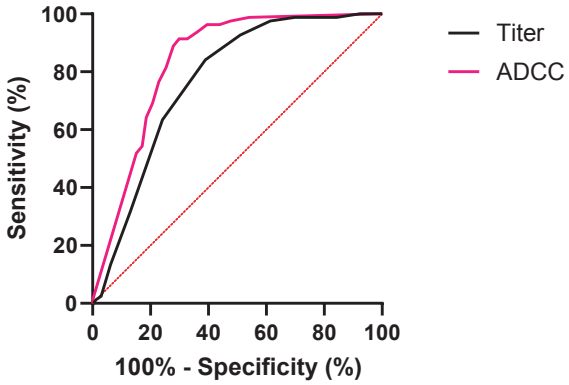

Figure 2: Receiver operating characteristics curve of the maximum maternal titer and ADCC for exchange transfusions in D-mediated HDFN.

National questionnaire on use of exchange transfusions

A total of 58 of 72 hospitals (82.8%) responded to the questionnaire, including all nine NICUs and 49 non-NICU hospitals. Thus, 14 non-NICU hospitals (17.2%) did not respond to the questionnaire.

Among the 49 non-NICU hospitals that responded to the questionnaire, 18 (36.7%) reported performing ETs during the study period (Figure 3A), while almost all (41/49 (83.7%)) performed the intervention before 2010. This represents a decline of 56.1% in the number of non-NICU hospitals currently performing ETs.

The 23 centers that stopped performing ETs reported a total of 33 reasons (Figure 3B). The most common reason that centers stopped performing ETs was due to centralization of care with regional agreements to transfer neonates with an impending ET to a NICU due to decreasing levels of experience (8/33, 24.2%), shortage of staff to perform ETs (8/33, 24.2%), loss of expertise due to rarity of the procedure (6/33, 18.2%), unavailable resources to perform ETs (6/33, 18.2%) and ETs being too time-consuming (5/33, 15.2%).

As part of a hypothetical question among the 31 centers that currently do not perform ETs, the majority (13/31 (41.9%)) reported being prepared to deliver a neonate and able to start intensive phototherapy followed by a potential transfer in case of an impending ET, irrespective of the antenatally determined risk of an ET. Eight centers (25.8%) at a risk of ≤20%, six centers (19.4%) at a risk of ≤10%, and lastly two centers (6.5%) at a risk of ≤5%. Two centers did not report on this item.

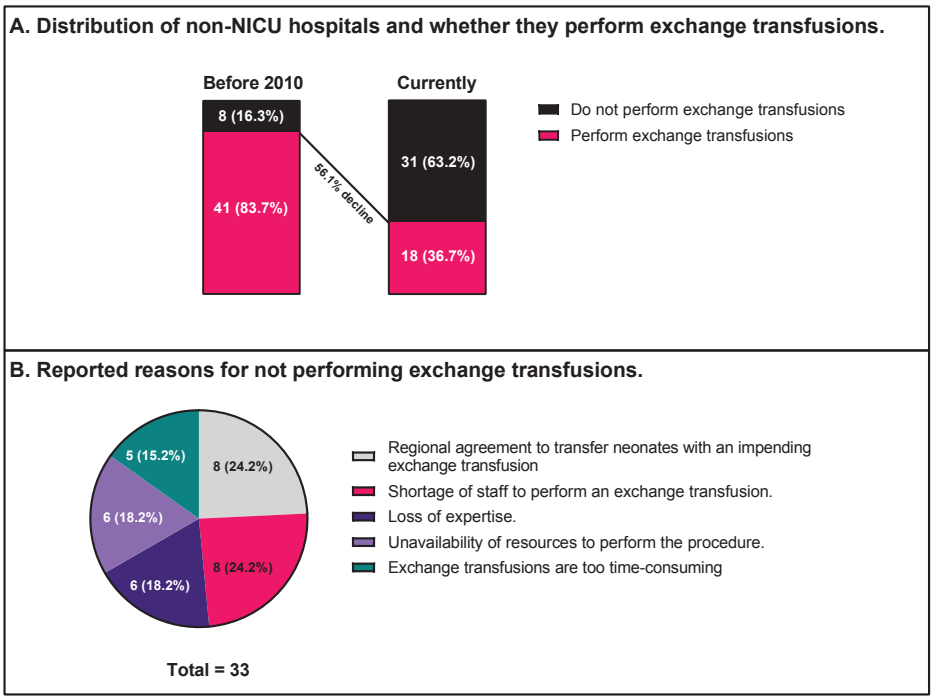

Figure 3: Distribution of non-NICU hospitals and whether they perform exchange transfusions, and the reported reasons for not currently not performing exchange transfusions.

DISCUSSION

This national multicenter study shows that antenatal tests (ADCC and maternal alloantibody titers) can be used by caregivers to anticipate the need for ET in neonates with non-ABO HDFN. The importance of an antenatal estimation of ETs is highlighted by the drastic decrease in the past two decades of the number of hospitals performing ETs. We identified a highly variable preparedness of pediatricians to treat neonates with a predetermined risk of an ET.

Our data showed increasing ET frequencies with increasing titer levels in pregnancies with D-alloimmunization reaching up to 19.6% in maximum maternal titers of 1:512, with a relative decline to 13.6% in maximum maternal titers of 1:1024 or above. This decline in ET frequency is likely to be related to the proportion of neonates treated with IUTs, as multiple IUTs are known to be associated with a lower risk of ETs.15 These findings are similar to a previous study on the diagnostic value of the ADCC and titer for the prediction of fetal anemia in a cohort from 1991 until 1995.[11] Importantly, we found that the maximum maternal ADCC test could further stratify the ET frequency in D-mediated HDFN with a considerably lower frequency in ADCC values below 50% despite high

maternal titers. Such findings could not be replicated for c-alloimmunization, because of limited numbers and missing data, despite this multicenter study. Our findings may aid in determining the optimal place of birth, in which high-risk cases may be pre-emptively delivered and treated in centers that perform ETs. This would limit delays in treatment and avoid the need for transport of cases with severe hyperbilirubinemia from centers that do not perform ETs. Moreover, neonates with a predetermined lower risk of ET may be delivered in hospitals that do not perform ETs but are able to start intensive phototherapy and transfer the neonate in case of an impending ET. The study's findings are currently being implemented in the Dutch obstetric and pediatric guidelines for the management of HDFN. However, the ADCC is currently solely performed in the Netherlands due to its complexity and use of radioactive material, limiting the generalizability of our findings and urging the field to explore new assays to estimate in-vivo hemolytic activity.

It has previously been shown that the improved application of intensive phototherapy and increased thresholds for ETs have led to considerably decreased ET rates in neonates with HDFN.[6-10] Implementation of new guidelines, such as the American Academy of Pediatrics guideline for the management of hyperbilirubinemia 2022[16], may lead to a further decline in ET rates due to higher thresholds for ETs.

Although no data exists on the optimum number of ETs to be performed to acquire or uphold procedural expertise, the increasing rarity of ETs will likely lead to less exposure, thereby potentially leading to a loss of expertise on a national level. This is also reflected in the findings from the questionnaire in which we found that more than half of the non-NICU hospitals currently do not perform ETs. Among these nearly 50% report that they did perform ETs before 2010. This decline seems mainly attributable to the rarity of the procedure and the lack of available healthcare professionals and materials as reported by these centers.

These findings further necessitate an urgent dialogue on the need for antenatal identification of at-risk neonates, regional agreements on the management of high-risk pregnancies and the management of severe hyperbilirubinemia along with continued efforts in the training, education, and awareness among pediatricians and pediatric residents. Additionally, neonatologists and neonatal fellows ought to be trained in the preparation and performance of ETs, as well as monitoring for and the management of procedure-related complications, to ensure that the next generation of pediatricians has adequate training and exposure to such clinical situations and can guarantee timely treatment of neonates with severe hyperbilirubinemia in the future. This may be hampered, however, as no validated simulation training for ETs currently exists.[17,18] ETs

are highly specialized procedures that are less commonly required in contemporary practice and should, thus, be conducted in specialized centers with a concentration of clinical experience.

This study and the interpretation of its findings are limited by the retrospective study design and its reliance on available data. Yet, through the national centralization of laboratory and clinical care for HDFN, and the joint collaboration of 24 centers, including all NICUs, we were able to gather unique data on a rare disease on a national level and may thereby provide a framework for other countries to carry out similar endeavors. Moreover, prospective data collection in this setting may not be feasible due to the rarity of the disease and ETs for HDFN. Even though 55% of the hospitals that had ordered an ET product in the study period did not participate in the study, the 24 participating centers ordered the vast majority (84%) of all ET products within the study period. It is possible, however, that a small number of neonates with HDFN may have been missed. Furthermore, 17% of hospitals did not respond to the questionnaire. Nevertheless, we expect that the calculation of the decline in the number of hospitals performing ETs was not impacted by this limitation. Lastly, based on the available data we were unable to establish an optimal timing of serological testing to antenatally determine the risk for an exchange transfusion. To overcome this challenge, we used the maximum maternal serological test results that are generally ceased once critical values are reached.

In conclusion, overall reductions in ET frequency have led to an altered treatment landscape, with fewer pediatricians currently being able to perform this invasive and complex procedure. Antenatal determination of maternally alloantibody titers and ADCC may aid caregivers in anticipating the postnatal severity of hyperbilirubinemia and the risk for an ET.

REFERENCES

1. De Winter DP, Hulzebos C, Van 't Oever RM, De Haas M, Verweij EJT, Lopriore E. History and current standard of postnatal management in hemolytic disease of the fetus and newborn. European Journal of Pediatrics 2023; 182(2): 489–500.
2. van 't Oever RM, Zwiers C, de Winter D, et al. Identification and management of fetal anemia due to hemolytic disease. Expert Review of Hematology 2022; 15(11): 987–98.
3. Delaney M, Matthews DC. Hemolytic disease of the fetus and newborn: managing the mother, fetus, and newborn. Hematology 2014, the American Society of Hematology Education Program Book 2015; 2015(1): 146–51.
4. de Haas M, Thurik FF, Koelewijn JM, van der Schoot CE. Haemolytic disease of the fetus and newborn. Vox Sanguinis 2015; 109(2): 99–113.
5. Lucey J, Ferreiro M, Hewitt J. PREVENTION OF HYPERBILIRUBINEMIA OF PREMATURITY BY PHOTOTHERAPY. Pediatrics 1968; 41(6): 1047–54.
6. Ree IMC, Besuden CFJ, Wintjens V, et al. Exchange transfusions in severe Rh-mediated alloimmune haemolytic disease of the foetus and newborn: a 20-year overview on the incidence, associated risks and outcome. Vox Sang 2021; 116(9): 990–7.
7. Steiner LA, Bizzarro MJ, Ehrenkranz RA, Gallagher PG. A decline in the frequency of neonatal exchange transfusions and its effect on exchange-related morbidity and mortality. Pediatrics 2007; 120(1): 27–32.
8. Hemmati F, Mahini SM, Bushehri M, Asadi AH, Barzegar H. Exchange Transfusion Trends and Risk Factors for Extreme Neonatal Hyperbilirubinemia over 10 Years in Shiraz, Iran. Iran J Med Sci 2024; 49(6): 384–93.
9. Wolf MF, Childers J, Gray KD, et al. Exchange transfusion safety and outcomes in neonatal hyperbilirubinemia. J Perinatol 2020; 40(10): 1506–12.
10. Bujandric N, Grujic J. Exchange Transfusion for Severe Neonatal Hyperbilirubinemia: 17 Years' Experience from Vojvodina, Serbia. Indian J Hematol Blood Transfus 2016; 32(2): 208–14.
11. Oepkes D, van Kamp IL, Simon MJG, Mesman J, Overbeeke MAM, Kanhai HHH. Clinical value of an antibody-dependent cell-mediated cytotoxicity assay in the management of Rh D alloimmunization. American Journal of Obstetrics and Gynecology 2001; 184(5): 1015–20.
12. Koelewijn JM, Slootweg YM, Folman C, van Kamp IL, Oepkes D, de Haas M. Diagnostic value of laboratory monitoring to predict severe hemolytic disease of the fetus and newborn in non-D and non-K-alloimmunized pregnancies. Transfusion 2020; 60(2): 391–9.
13. Hyperbilirubinemia So. Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics 2004; 114(1): 297–316.
14. de Winter DP, Lopriore E, Hulzebos CV, et al. Use and Waste of Reconstituted Whole Blood Exchange Transfusions: An 11-year National Observational Study. J Pediatr 2024: 114225.
15. Ree IMC, Lopriore E, Zwiers C, et al. Suppression of compensatory erythropoiesis in hemolytic disease of the fetus and newborn due to intrauterine transfusions. American Journal of Obstetrics and Gynecology 2020; 223(1): 119.e1–.e10.
16. Kemper AR, Newman TB, Slaughter JL, et al. Clinical Practice Guideline Revision: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics 2022; 150(3).
17. Maldonado MJ, Agudelo SI, Suarez JD, Gamboa O. Educational strategy for the development of skills in exchange transfusion: a randomized clinical trial protocol. Trials 2020; 21(1): 387.
18. Rosen O, Angert R. Exchange Transfusion Simulation Models: A Technical Report. Cureus 2019; 11(8): e5317.

SUPPLEMENTAL FILES

Supplemental Table 1: Alphabetical outline of all participating centers and investigators
Supplemental Table 1 provides an outline of all participating centers, whether it concerns a neonatal intensive care unit (NICU), and the investigators from that participating center.

Participating Center	NICU	Investigators
Amphia Ziekenhuis	Non-NICU	Ron van Beek, A.J. (Adriaan) van Gammeren
Amsterdam University Medical Center	NICU	Sandra A. Prins, J.H. Klinkspoor
Deventer Ziekenhuis	Non-NICU	
Erasmus Medisch Centrum	NICU	Jasper V. Been, Henk Russcher
Flevoziekenhuis	Non-NICU	Clare E. Counsilman, Sietske Hogenboom
Franciscus Gasthuis & Vlietland	Non-NICU	Huib Ceelie, Angelique Hoffmann-Haringsma
Groene Hart Ziekenhuis	Non-NICU	Gerdina H. Dubbink-Verheij, Jacques J.H. Hens
Isala Zwolle	NICU	Esther J. d'Haens, Gijs den Besten
Jeroen Bosch Ziekenhuis	Non-NICU	Lieke M.J. van Zogchel, N.C.V Péquériaux
Leiden University Medical Center	NICU	Derek P. de Winter, E.J.T. (Joanne) Verweij, Masja de Haas, Enrico Lopriore
Maasstad Ziekenhuis	Non-NICU	Helene G. Stas, Floor Weerkamp
Maastricht University Medical Center	NICU	Amanda M.P. Trompenaars, Tinta J.F. Lebon
Maxima Medisch Centrum	NICU	Annemiek M.C.P. Joosen, Peter Andriessen
Meander Medisch Centrum	Non-NICU	Clemens B. Meijssen, Karlijn Gijzen
Medisch Centrum Leeuwarden	Non-NICU	F.R. Knol
Noordwest Ziekenhuisgroep	Non-NICU	Janneke C. Zant, Geert Jan Blok
Radboud Universitair Medisch Centrum	NICU	Sabine L.A.G. Vrancken, Annegeet van den Bos
Rijnstate ziekenhuis	Non-NICU	Maaike C. van Rossem, Jolanda Lamberts
Slingeland ziekenhuis	Non-NICU	
Spaarne Gasthuis	Non-NICU	I.A.M. Schiering, Claudia Admiraal
St. Antonius ziekenhuis	Non-NICU	J.L.A.M. van Hillegersberg
Universitair Medisch Centrum Utrecht	NICU	Daniël C. Vijlbrief, Karen M.K. De Vooght
Universitair Medisch Centrum Groningen	NICU	Christian V. Hulzebos, Michaël V. Lukens

Questionnaire to identify hospitals that currently perform exchange transfusions and to evaluate the preparedness of caregivers to deliver neonates at-risk of exchange transfusions

English translation of the Dutch questionnaire.

1. At what center are you currently employed?*

_____

2. Is your center a post-intensive care or high-care center?*
   One answer possible
   ☐ Yes
   ☐ No
   ☐ Other:_____

3. Are exchange transfusions for neonatal hyperbilirubinemia performed at your center?
   One answer possible
   ☐ Yes (*go to question 6)*
   ☐ No (*go to question 4)*
   ☐ Other:_____

4. What is the main reason for your center **not** performing exchange transfusions for neonatal hyperbilirubinemia?
   Multiple answers possible
   ☐ Equipment to perform an exchange transfusion are not readily available
   ☐ Cannot place or use central lines at our center
   ☐ Cannot monitor for vital functions during the procedure at our center
   ☐ Takes too much time to perform an exchange transfusion
   ☐ Too few caregivers to perform an exchange transfusion
   ☐ Unknown or unaware how exchange transfusions products can be requested
   ☐ Other:_____

5. If in the future the probability of an exchange transfusion in neonates with D-alloimmunization can be estimated antenatally based on laboratory and clinical characteristics, at what chance of an exchange transfusion would your center be willing to deliver a child, provide intensive phototherapy and, if necessary, transfer in case of an impending exchange transfusion?
   One answer possible
   ☐ Higher than 20%
   ☐ 20% or lower
   ☐ 15% or lower
   ☐ 10% or lower
   ☐ 5% or lower
   ☐ Other:_____

Go to question 8

6. What sources of information does your center use for exchange transfusions?
   Multiple answers possible
   ☐ No sources of information are used at our center
   ☐ The guideline for the management of hyperbilirubinemia from the Dutch pediatric society (NVK richtlijn hyperbilirubinemie)
   ☐ Through the website www.babyzietgeel.nl
   ☐ International guidelines (for example the American Academy of Pediatrics or NICE guideline)
   ☐ Neonatology text books
   ☐ Other:_____

7. In case of an exchange transfusion, do you perform this after consulting your regional neonatal intensive care unit?
   One answer possible
   ☐ Yes
   ☐ No
   ☐ No, our department is a neonatal intensive care unit

8. Were exchange transfusions for neonatal hyperbilirubinemia performed at your center before 2010?
   One answer possible
   ☐ Yes
   ☐ No
   ☐ Other:_____